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August 18, 2003 — Date

Monica A. De La Paz

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Xiang et al.

Serial No.: 09/828,498

Filed: April 5, 2001

For: FULL-LENGTH GB VIRUS C (HEPATITIS G VIRUS) RNA TRANSCRIPTS ARE INFECTIOUS IN PRIMARY CD4 POSITIVE T CELLS AND METHODS OF TREATING HIV

Group Art Unit: 1648

Examiner: Winkler, Ulrike

Atty. Dkt. No.: IOWA:030US

SECOND DECLARATION OF JACK T. STAPLETON, M.D.

I, Jack T. Stapleton declare:

1. I am one of the inventors on the above-referenced patent application.

2. I am a citizen of the United States. I reside at 602 Clark St., Iowa City, Iowa 52240.

3. I am a Professor at the University of Iowa in the Department of Internal Medicine. I am also the Director of the University of Iowa HIV Program and the Director of the Helen C. Levitt Center for Viral Pathogenesis and Disease. I am a staff physician at Iowa City V.A. Medical Center. I have been conducting research in the area of infectious diseases, including hepatitis viruses such as GBV-C, for more than 19 years.

4. I understand that the claims in the above-referenced patent application have been rejected in the most recent Office Action as lacking novelty based on a number of references, including U.S. Patent 5,856,134 ("Kim reference").

5. Genelabs, Inc., which I understand owns the U.S. patent known as the Kim reference, requested that I test whether a clone disclosed in the Kim reference was infectious. I was told by Dr. Kim that this clone was not constructed before 2002, and that neither the clone nor the serum from which the clone was prepared were ever tested for infectivity.

6. Consequently, I was provided with a clone from Dr. Kim and Genelabs which linked the small fragments described in the Kim reference and on GenBank ("the Kim reference clone"). Genelabs called this clone 3ZHGV-6. Additionally, I was provided with a sample of serum from which the Kim reference clone was obtained, which was identified as PNF2161.

7. My laboratory performed assays on the Kim reference clone to determine whether the Kim reference clone is infectious, that is, capable of yielding a GBV-C particle from a transfected cell. These experiments were similar to those described in Examples 4 and 5 of the present patent application. In particular, RNA was transcribed from the plasmid DNA and transfected by multiple transfection protocols (lipofection, DEAE, electroporation) into primary peripheral blood mononuclear cells (PBMCs). These cells were fed weekly with fresh healthy donor PBMCs and culture supernatants monitored for evidence of GBV-C production by measuring GBV-C RNA in the culture supernatants. None of the samples obtained 2 or more weeks post-transfection demonstrated production of GBV-C RNA.

8. Thus, the Kim reference clone was not found to be infectious as GBV-C virus particles could not be recovered from cells transfected by the Kim reference clone.

9. Subsequent to our filing of this patent, we found that many serum samples from GBV-C infected people do not yield infectious viruses when cultured in PBMCs or other cell lines (see George *et al.*, In Press, Virology; attached as **Exhibit 1**), and the serum from which the Kim reference clone was derived did not yield persistent infection. Consequently, we performed infectivity testing on the serum sample (PNF2161) from which the Kim reference clone was obtained to determine whether the serum sample was infectious. These experiments were similar to those that are described in the attached reference. More specifically, serum was added to PBMCs and culture supernatants were monitored for evidence of GBV-C RNA production over time.

10. Thus, the serum sample tested did not yield GBV-C virus particles, further providing evidence that the Kim reference clone is not infectious.

11. Thus, none of the materials from Genelabs was infectious based on the assays performed. Furthermore, at this time I am unaware that Genelab has any other putative infectious clones.

12. I hereby declare that all statements made of my own knowledge are true and all statements made on information are believed to be true and further that the statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under § 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of this application or any patent issued thereon.

August 14, 2003
Date

Jack T. Stapleton, M.D.